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The effect of rapid loading and constant infusions on the plasma hydrocortisone concentration

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THE EFFECT OF RAPID LOADING AND CONSTANT
INFUSIONS OF HYDROCORTISONE ON THE PLASMA
HYDROCORTISONE CONCENTRATION

James Scheuer

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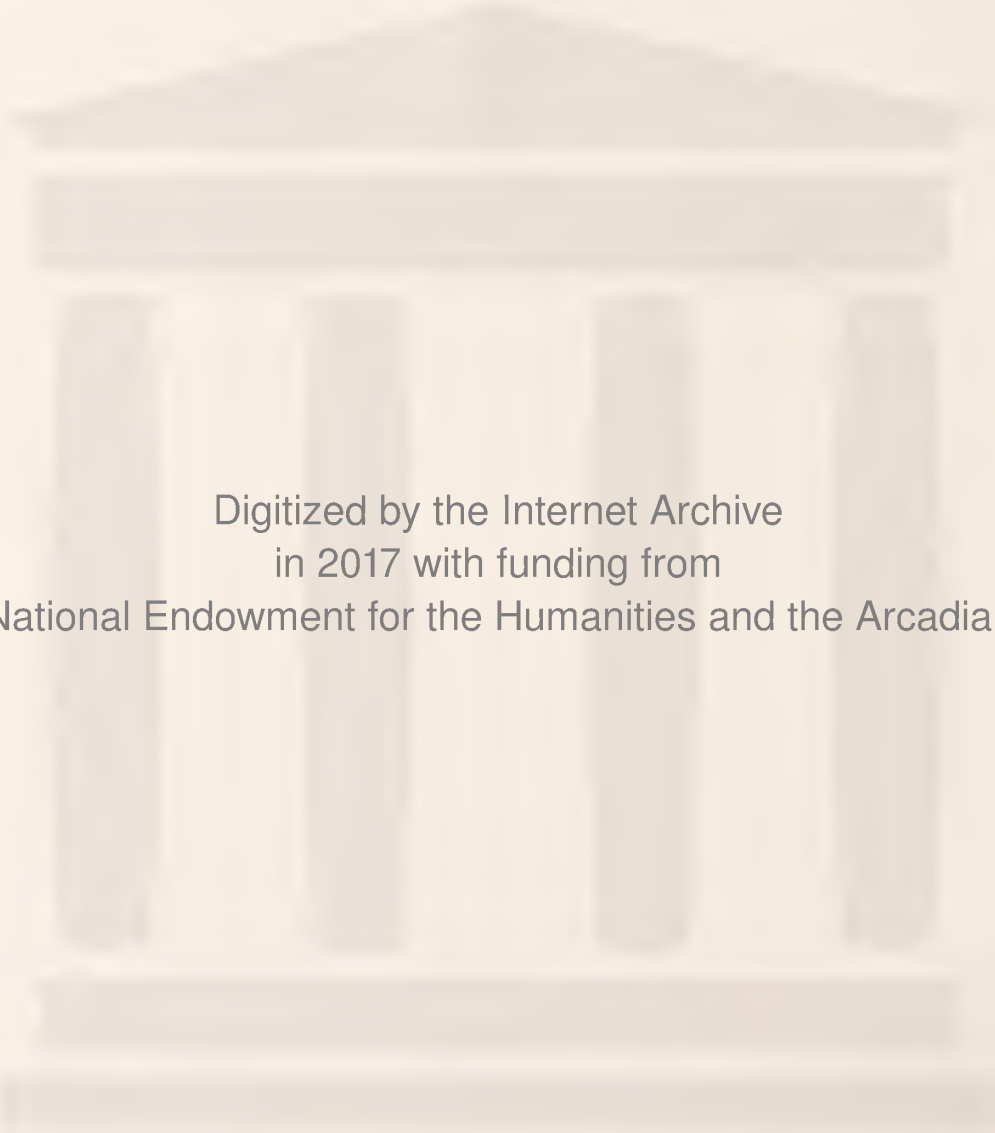
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THE EFFECT OF RAPID LOADING AND CONSTANT INFUSIONS OF HYDROCORTISONE
ON THE PLASMA HYDROCORTISONE CONCENTRATION

James Scheuer
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A.B. The University of Rochester, 1953

A Thesis Presented to the
Faculty of the Yale University School of Medicine
in Candidacy for the Degree of
Doctor of Medicine

Department of Internal Medicine
Yale University School of Medicine

1956



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INTRODUCTION

Ever since 1948, when Corcoran and Page introduced their method for the determinations of plasma steroids (17) many workers have directed their efforts to the perfection of steroid analysis and the correlation of physiological effects with plasma steroid levels under clinical and experimental conditions. Important methodological advances have been made since that time. Much effort has been directed to the analysis of free hydrocortisone in the plasma, because many workers have shown that this is the predominant glucocorticoid secreted by the human adrenal gland (14,27,48,57). Methods for this analysis have been as numerous as laboratories conducting research in the field. Significant advances were recorded by Porter and Silber (40), whose quantitative color reaction with phenylhydrazine hydrochloride was adopted by many workers, and which, with modifications, is still the basis of some methods. Nelson and Samuels (34), Bush (13), Morris and Williams (33), Bondy and Altrock (8), Kassenaar et al. (28), and Weichselbaum et al. (63), to mention just a few, all found it necessary to process plasma by extraction followed by purification of the extract and use the Porter-Silber or other reactions for quantitation of the purified substance. Most of these methods are time consuming, intricate procedures involving numerous steps with various solvents and precipitates for extraction, usually followed by column chromatography for purification. Bush (13) has purified the extract with paper chromatography. Only recently Wallace et al. (62) published a simplified method well suited to

clinical work but at the expense of the high degree of accuracy needed for experimentation. The method of Nelson and Samuels has been the most widely used procedure up to the present time. Recently Bondy et al. (7) have used a method involving paper chromatography for purification of a chloroform extract of plasma. The main advantage of this method lies in the fact that the extraction procedure is simple and relatively pure hydrocortisone can be isolated on paper, free from the contaminants usually added by columns, and separated from other steroids that might run in the hydrocortisone fraction.

Because of the very low concentrations of plasma steroids their quantitation has been a challenging problem. Methods introduced by Corcoran and Page (17) depend on the presence of the ketol side chain, as does the Porter Silber phenylhydrazine hydrochloride reaction (40). Bush (13) quantitated his paper spots by their reaction with iodine. Recently methods that use the fluorescent properties of Δ^4 -3-ketosteroids in acid or alkaline solutions have been developed for the accurate determination of small amounts of purified steroids (1,55). The advantage of these procedures is that results are readily reproducible at low concentrations, and they are specific for those steroids which have the Δ^4 -3-configuration in ring A.

Since the advent of improved methods many studies have been done to determine the fate of hydrocortisone and correlate plasma levels with metabolic effects in normal humans and persons under various clinical and test situations (2,24,29,31,37,39,47,50,61). In 1951, Nelson et al. (35) and later Bliss (6) and Bayliss (4)

determined the normal values for circulating 17-hydroxycorticosteroids, and more recently Bondy (7) has repeated this work with the analytical method used in this study. Much has been done to determine the effects of ACTH on blood levels of hydrocortisone (4,5,15,20,35,41) and urinary levels of the steroid metabolites (44). There have been studies on the effects of hydrocortisone (16,23,43), its role in electrolyte balance (30), amino acid metabolism (9,58), and composition of urine (12,26,42,46,52), just to mention a few. The action of certain drugs and hormones on hydrocortisone metabolism has been the subject of other studies (18,25,51), along with the effects of hydrocortisone on the function of other hormones (38).

In 1952, Nelson et al. (36) gave 200 mg. of oral hydrocortisone to humans and noticed a rise in the blood level, which fell to normal in eight hours. They also observed similar effects after intramuscular injections of ethanolic solutions of hydrocortisone. Richards and Sweat (45) observed a consistent rise to about 50 ug. percent in 45 to 60 minutes after the oral administration of 50 mg. of hydrocortisone, and Haynes (25) gave 50 mg. orally and noticed a three hour peak and a five hour fall to normal. In all of these experiments the route of administration required an unmeasured amount of time for absorption which introduced a large variable. Eik-Nes (20) noticed after ACTH induced an elevation of the blood 17-hydroxycorticosteroid concentration it decreased at a rate proportional to the concentration. Using C-14 labelled hydrocortisone as a tracer dose, Hellmann et al., in 1954 (26) gave a total of

100 mg. of hydrocortisone intravenously over a thirty minute period and studied the rate of disappearance of labelled carbon from the blood and its excretion in the urine, feces, and expired air. The percentage of excretion of C-14 was constant with time, no matter how much carrier hydrocortisone was used. Fifteen minutes after the infusion was stopped only 13 percent of the radioactivity was present as free hydrocortisone. In 1954, Brown et al. (11) gave intravenous hydrocortisone, 1 mg. per Kg. over a thirty minute period, and found that after one hour the plasma 17-hydroxycorticosteroid level fell exponentially. Eik-Nes et al. (21) gave 50 mg. of hydrocortisone intravenously in a two minute period and derived a mean curve from which a half-life of about two hours can be calculated. Done (19) studied the half-life of hydrocortisone after intravenous injection in normals and patients with rheumatic fever and found a range in normals of 60 to 133 minutes with an average of 90 minutes. The disappearance curve after the administration of 1 mg. per Kg. over a thirty minute period was proportional to the concentration in the plasma, thus appearing to be a first order reaction. Sayers' group (53) showed an initial period of rapid removal from the blood, immediately after the infusion, followed by a period of disappearance at a rate proportional to concentration, with half-lives of 1.3 to 2.3 hours in one normal and two Addisonian patients. Peterson et al. (39) found a half-life in 20 normals of 114 ± 6.5 minutes with a range of 90 to 130 minutes after administration of 50 to 500 mg. over about a thirty minute period.

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In this project we have been interested in studying the intimate mechanics of the disappearance of intravenous hydrocortisone. Disappearance curves of hydrocortisone have been determined, both after acute massive levels in Part I, and during slow injections at rates which permitted the establishment of equilibrium at plasma hydrocortisone concentrations found clinically in Part II. Because we have administered all the hydrocortisone at one time in Part I, we have been able to study the early period of rapid removal from the plasma, which has not been done in previous experiments. By administering a smaller dose over a long period and at a constant known rate we have been able to reach a time when the amount of hydrocortisone entering the plasma equals the amount leaving it. Therefore the decay at this time should equal that of hydrocortisone at equilibrium. We have also attempted to estimate the volume of distribution of hydrocortisone in the body assuming that it is at a constant concentration throughout its distribution.

MATERIALS AND METHODS

All subjects were healthy male medical students between the ages of 21 and 25 years, without evidence of serious disease, or history of hepatic, renal, or endocrinological abnormality. Studies were started between 8:30 and 9:30 A.M. The subjects were ambulatory, but were kept at a low level of physical activity. They were on normal diets throughout the experiment, and all understood the nature of the procedure. Five subjects were used in each part, and those who participated in Part I were not used in Part II.

Heparinized blood samples were centrifuged immediately upon withdrawal and except in a few cases were extracted the same day. On occasion it was necessary to freeze the plasma for a few days prior to extraction. The plasma samples were analyzed by the method of Bondy et al. (7), a brief description of which follows.

Appropriate duplicate quantities of plasma were mixed with 0.5 ml. of 1.0 normal NaOH per 20 ml. of plasma, and with 1.0 ml. of C-14 labelled hydrocortisone, with about 400 counts per minute. They then were extracted three times with 20 ml. of freshly distilled chloroform and transferred to boiling flasks, with a small well at the bottom, dried down, and the dried extract washed into the well with chloroform. The well contents were then spotted on Whatman's no. 1 chromatography grade filter paper by using a few drops of chloroform as the transferring solvent. The paper was then placed in a Bush toluene-75 percent methanol chromatography

system, allowed to equilibrate overnight and then having a toluene mobile phase run with gravity for four hours. The hydrocortisone spots were identified by taking a contact picture with a short wave ultra violet light, "Mineralight" model SL 2537, for one second at a distance of nine feet. The spots were then cut out in parallel with a paper blank of identical size just distal to the hydrocortisone spot and were eluted in 3 ml. of absolute ethyl alcohol at 40 degrees centigrade for one hour. Three tenths ml. aliquotes were dried down in duplicate fluorimetry tubes and a standard curve made up with 0.5, 1.0, and 2.0 ug. of pure hydrocortisone. One half ml. of 0.30 to 0.35 normal potassium tert-butoxide base in tert-butyl alcohol was added to each tube, and the fluorescence allowed to develop for one hour, then read on a Farrand fluorimeter, using a Corning No. 5860 primary filter and a Corning No. 2418 secondary filter. One ml. aliquots were dried down and dissolved in 15 ml. of solvent made up with 4.0 gm. of 2,5-diphenyloxazole and 0.03 gm. of 1,4-di [2-(5 phenyloxazol)] benzene per liter of toluene and then counted in a Technical Measurement Corporation liquid phosphor counter, LP-2A, and percent radioactive recovery calculated by comparing the number of counts per sample with a standard that had been measured out on the day of the extraction procedure. The percent recovery was used to correct for hydrocortisone lost during the analytical procedure. The corrected value was then translated into micrograms percent. The calculated standard deviation between duplicate samples is \pm 10 percent.

EXPERIMENTAL PROCEDURES

Part I.: A control blood specimen was drawn using a no. 19 needle, and 100 mg. of hydrocortisone in 20 ml. of 50 percent alcohol (Upjohn) which had been diluted up to 150 ml. with 5 percent glucose in water, was injected over a five minute period through the same needle. Blood samples were taken at 15, 60, 150, 300, and 420 minutes. In two subjects samples were taken every fifteen minutes for the first hour and every twenty minutes for the second hour. The total amount of blood drawn was 320 ml.

Part II.: After a control blood specimen was drawn, an infusion of hydrocortisone in 500 ml. of 5 percent glucose (Merck) was injected at approximately 300 ug. per minute, using a constant infusion pump and infusing through a no. 19 needle. Thereafter blood was withdrawn from the opposite arm at 60, 165, 180, 300, and 480 minutes. The total amount of blood drawn was 360 ml. After withdrawal of the 180 minute sample the infusion was stopped and the solution run through the pump and needle into a 100 ml. volumetric flask for ten minutes. The flask was then filled to volume with distilled water, and an appropriate aliquot was extracted with chloroform three times, the chloroform dried down, the residue dissolved in 6 ml. absolute ethyl alcohol, and read on a Beckman spectrophotometer at a wave length of 242 m μ to determine accurately the amount of hydrocortisone infused over a ten minute period.

CALCULATIONS

Part I.: Curves were plotted on semi-logarithmic graph paper. At the time of the first post infusion sample it was assumed that the adrenal gland was no longer secreting hydrocortisone and that the amount of endogenous hydrocortisone present was relatively small so that the plasma level was almost totally due to exogenous hydrocortisone. If the volume of distribution of the steroid is constant and the rate of disappearance from the plasma is proportional to concentration (21) the rate is represented by the equation:

$$1. \quad \frac{dc}{dt} = kc$$

Where "c" is the concentration in the volume of distribution, "t" is time, and "k" is the percent of steroid disappearing per unit time. By integrating we get:

$$2. \quad c = C_0 e^{-kt}$$

Where "C₀" is the concentration at time zero.

Part II.: Curves were plotted on linear and semi-logarithmic graph paper. The same assumptions were made regarding the endogenous hydrocortisone as in Part I. Since hydrocortisone was being added to the system at a constant rate the change of concentration assuming no loss would be:

$$3. \quad \frac{dc}{dt} = \frac{Q}{V}$$

Where ℓ is rate of infusion and "v" the volume of distribution. When the rate of disappearance of the steroid is taken into account (equation 2), the net increase in concentration may be represented by:

$$4. \quad \frac{dc}{dt} = \frac{\ell}{v} - kc$$

If the concentration of material was zero at time zero, then integrating:

$$5. \quad c = \frac{\ell}{kv} (1 - e^{-kt})$$

When "t" reaches infinity "c" reaches an asymptote:

$$6. \quad c = \frac{\ell}{kv}$$

ℓ is a known constant and the values for "c" are known at different times. Substituting these values in equation 5, "v" and "k" can be derived, and by equation 6, "v" can be derived when "c" has reached the asymptote. The descending curve is analyzed by equation 2.

We calculated the elimination of endogenous hydrocortisone in Parts I and II from equation 2, assuming that the disappearance of endogenous hormone proceeded at the same rate as exogenous hydrocortisone when at equilibrium (26). By subtracting the calculated endogenous curves from the total one obtains an approximation of the exogenous curves (figures 1,2, and 3).

RESULTS

Table 1 represents the levels obtained after the acute injection. The concentrations differ widely about the mean, but each falls on a smooth curve. Figure 1 represents the mean graph of Part I. During the first 150 minutes the rate of disappearance from the plasma decelerates fairly evenly and forms a curve on semi-logarithmic paper. It can be represented by two arbitrary straight lines which approximate the average rates of disappearance during those periods. Thus during the first 60 minutes there is a rapid disappearance from the plasma at an average rate of 1.84 percent per minute. Over the next 90 minutes the disappearance averages 1.20 percent per minute. For the next 270 minutes the disappearance rate remains constant at 0.51 percent per minute with a mean half-life of 138 minutes and a range among our subjects of 58 to 161 minutes.

Frequent samples were taken during the first two and a half hours in two subjects. The results are shown in Table 2. Because of the very high exogenous levels during this early part of the curve it is not necessary to subtract the endogenous levels. During this time there is a rapid fall, especially in subject JS where the concentration falls precipitously and then rebounds upward to approach the mean curve. The magnitude of this fall is much greater than experimental error, since the standard deviation for this part of the curve was ± 8.5 percent. The number of subjects is too small and the results too individualized to permit calculation of relevant

half-lives; however, the data demonstrates the rapidity of the fall and un predictability of the disappearance curves immediately after a large hydrocortisone injection. If one assumes that the plasma volume is 4 percent of body weight, in these experiments 94.0 percent of the administered dose had disappeared from the plasma after 15 minutes, 97.4 percent at the end of 60 minutes, and 99.1 percent after 150 minutes.

The plasma hydrocortisone level fell below the initial endogenous concentration five to seven hours after the acute hydrocortisone injection.

Table 3 represents the results obtained with the constant infusion in Part II. Here, as in Part I, there is a wide individual variation from the mean. The values at 165 minutes and 180 minutes are so similar for any given subject that it has been thought valid to average them and consider that the curve has reached its asymptote during this period. The equilibrium concentrations range from 23.6 to 62.6 μ g. percent. During the infusion the rate of utilization of hydrocortisone decreases constantly, leveling off during the final 15 minutes toward a half-life of 172 minutes. During this 15 minute period, the volume of distribution averages 116 percent of body weight. Figure 2 shows the calculated mean curve plotted on linear graph paper and the theoretical curve one would obtain if "k" were equal to that during the post infusion period, when it is constant, and if "v" is derived from equation 6, when "c" has reached the asymptote. This calculation for "v" comes out 186 percent of body

weight. In Part II the hydrocortisone disappears from the blood at a constant rate of 0.57 percent per minute with a half-life of 124 minutes and an individual range of 93 to 141 minutes. During the infusion, 96.7 percent of the administered hydrocortisone had disappeared from the plasma after 60 minutes and 97.9 percent after 180 minutes.

Pre-infusion levels in all subjects in Part II, except TT, are above the normal range. Control samples at a later date are all within normal range. At the end of Part II, as in Part I, there is a dip in the plasma hydrocortisone level below the initial endogenous level.

DISCUSSION

In these experiments after a period of equilibration hydrocortisone disappeared from the blood stream at a constant rate, with an average half-life of about 130 minutes. This confirms the observations by Eik-Nes (20,21), Brown (11), Done (19), Sayers (53), and Peterson (39) previously referred to. This constant rate is due mainly to the activity of the liver since Tomizawa et al. (59) found hepatectomized rats did not metabolize hydrocortisone, and Brown (11) showed that in patients with liver disease the disappearance rate of hydrocortisone was slowed proportional to the retention of bromsophthalein, but that the tetra-hydro metabolite of hydrocortisone was eliminated normally. Weichselbaum (64) showed a greatly diminished ability of the liver to conjugate hydrocortisone in severe stress where there is a high hydrocortisone level. Peterson (39) also found increased half-lives in all his patients with liver disease.

Like Brown (11) and Hellman (26), we found that initially removal of hydrocortisone from the blood is very rapid. If the data presented by Eik-Nes (21) for individual curves is plotted on semi-logarithmic paper each curve falls more rapidly between the first and second hour than during the remainder of the time. During the first hour the hydrocortisone was leaving the plasma almost four times as fast as when at equilibrium. During this period, most of the hydrocortisone disappearing from the plasma was probably entering

the liver, for Braellow et al. (10) showed that 70 percent of infused hydrocortisone was quickly bound by the mouse's liver, but some of the steroid probably went elsewhere. Tomizawa et al. (59) showed a rapid ten minute fall of hydrocortisone levels after infusion in hepatectomized rats, followed by a period during which a high level was maintained. They attributed the ten minute fall to a period of equilibration after which any further decline was due to liver metabolism. Leven et al. (32) attributed this rapid disappearance phase to binding by tissues, and showed that in this property kidney, spleen, and liver were very active, whereas diaphragm and fat were less so. Of all these tissues, however, the liver was the only one that metabolized hydrocortisone to any significant degree. They postulated that bound steroid was in equilibrium and freely exchangeable with plasma steroid. There is also in vitro evidence of rapid binding of hydrocortisone by various proteins (22). The early rapid disappearance is probably due to many of these factors. We might postulate two general equations:

1. Free plasma hydrocortisone and receptor proteins \rightleftharpoons bound hydrocortisone.
2. Free plasma hydrocortisone $\xrightarrow{\text{liver}}$ reduced hydrocortisone.

Where plasma is loaded with hydrocortisone, reaction 1, which is normally at equilibrium, must shift to the right. As the products on the right accumulate up reaction 1 slows down until equilibrium

is again attained. Meanwhile reaction 2 goes on at a rate proportional to plasma concentration. Initially, therefore, the plasma concentration reflects both reactions, but during the later part of the experiment reaction 1 is at equilibrium and the plasma concentration curve represents reaction 2. Peterson (39) sites evidence for a specific liver enzyme which acts on hydrocortisone, and not other steroids, to reduce the Δ^4 double bond. This is the limiting reaction the dihydrohydrocortisone being quickly reduced by a non-specific enzyme to tetrahydrohydrocortisone.

In Part II the mean curve comes to equilibrium sooner than was predicted. It might be postulated that hydrocortisone is at equilibrium with a smaller space and does not yet fill the calculated "v" with "t" infinity. We found the experimental volume based on the rising curve to be less than the theoretical volume. The calculations predicting the plasma hydrocortisone curves during constant loading assume that the volume of distribution and the velocity constant "k" do not change. Actual observation, however, showed that either "v" or "k" or both changed constantly during the infusion. This may be, in part, because the concentration of hydrocortisone is not equal in the various body fluid compartments (3,49). From the two equations suggested above, one might anticipate that the value of "k" would be high early in the infusion, and fall toward a constant value as equilibrium of equation 1 is reached. This was, infact, observed. One might also predict that the hydrocortisone binding of proteins of equation 1 might be able to hold the steroid in higher concentration than does the plasma (22,34).

This deduction is supported by our calculations that "v" at equilibrium is greater than body volume, indicating that in some tissues hydrocortisone is more concentrated than in plasma. Similar calculations on the data from Tomizawa's hepatectomized rat experiment (59), where almost no hydrocortisone is being destroyed also show "v" to be greater than body volume. Peterson (39) estimated a hydrocortisone space that equaled body weight. Thus the concept of volume of distribution for hydrocortisone at a constant concentration is not a valid one.

The low values for hydrocortisone found at the end of the experiment can be interpreted as due to suppression of ACTH by exogenous hydrocortisone with a lag period after most of the hydrocortisone has been metabolized, leaving an adrenal that has had no stimulation for a few hours. There must be many unrecognized variables which act upon the distribution and disappearance of hydrocortisone to account for the wide range of individual values. Pre-injection steroid concentrations were frequently elevated in subjects later proven to be normal suggesting that the test situation itself may alter in some way either the rate of endogenous secretion or rate of utilization of the hormone. The detailed one hour curves in Part I indicate that these reactions may be multiply influenced, and may depend upon body functions controlled by other systems which alter the rate of equilibrium or degradation. In some individuals the initial fall is much steeper and the period of degradation more gradual. Post-infusion values are much higher in some individuals than others and not inversely related to body size.

Therefore the fact that the mean disappearance curves are so similar in two sets of subjects has only significance in showing that the disappearance of hydrocortisone after reaching equilibrium in the serum and at clinical levels is proportional to the concentration of hydrocortisone but varies greatly from one individual to the next.

The disappearance rate of exogenous hydrocortisone was remarkably constant in the two groups with different doses and rates of infusion. Peterson (39) showed that the rate of disappearance remains the same in an individual whether 50 or 500 mg. of hydrocortisone are infused. Thus at levels of hydrocortisone seen in Cushing's disease (14,37,56), pregnancy (47), during surgery (50), rheumatic fever (29), life threatening states and other clinical situations (37,54) there is a constant rate of disappearance in normals. The frequency of such a rise as part of the body reaction to disease and stress suggests that the mechanism of increased hydrocortisone levels may be similar in these unrelated states. Studies cited previously indicate that hydrocortisone degradation is slowed down in certain conditions due to decreased liver metabolism. However, that this is not always the mechanism of an increased level was shown by Tyler et al. (60) who found high concentrations in elderly normals who had normal rates of breakdown by the liver. They postulated a contracted volume of distribution with a normal output. In carcinoma of the adrenal neither liver metabolism or hydrocortisone space are responsible for the high level, which is probably due to the autonomy of the neoplasm and uncontrolled secretion. In stress the hydrocortisone levels are higher than can be accounted for by maximum ACTH production for

large amounts of ACTH cannot stimulate the normal adrenal to produce these levels (61). Thus the question of what controls hydrocortisone levels in the blood is far from answered. There may be many factors, some of which might include changes in hydrocortisone space and binding power of tissues; a change in the reactivity of the adrenal cortex to ACTH under different conditions; rate of autonomous secretion by the adrenal cortex; decreased peripheral utilization; and diminished liver metabolism. All of these must be studied before hydrocortisone metabolism can be well understood.

SUMMARY

1. Some of the highlights in the history of plasma corticosteroid chemical analysis are cited. Some previous experiments involving the effects of hydrocortisone, its metabolism, and rates of disappearance from the plasma are reviewed.
2. One hundred mg. of hydrocortisone was injected intravenously in five minutes into healthy subjects and the disappearance of the steroid from the plasma was followed. The rate of removal was rapid at first, gradually decreasing to about one-fourth of the original rate at two and one-half hours, after which it remained constant with a mean half-life of **138** minutes.
3. In a second set of experiments a constant infusion of 300 μ g. per minute was given. At three hours an equilibrium was reached where the amount leaving the plasma equaled the amount entering. The post infusion curve was plotted and a mean half-life of **124** minutes was found. The volume of distribution at the plasma concentration at equilibrium was 116 or 187 percent of body weight was found, depending on the method of calculation.
4. Large individual variations were noted in these experiments.
5. Levels a few hours after infusion were lower than those found before. Pre-infusion levels were elevated above normal in some of the subjects later proven to be normal.
6. The results suggest that hydrocortisone may leave the plasma in two general ways: by a reversible system in which the steroid is bound in high concentrations to tissue proteins,

and an irreversible system whereby hydrocortisone is permanently removed from the plasma. The early part of the disappearance curve is greatly influenced by the reversible binding of the steroid, whereas the late portion of the curve reflects a first order metabolic process, presumably occurring chiefly in the liver.

TABLE 1.

PLASMA HYDROCORTISONE LEVELS AFTER ACUTE INTRAVENOUS INJECTION OF HYDROCORTISONE

Part I: Uncorrected levels in $\mu\text{g. percent}$.

Subject	Weight	Time in minutes					
		0	15	60	150	300	420
CH	92.9 Kg.	10.0	140	84.0	14.5	2.5	8.2
AB	75.0	9.4	205	73.8	31.1	15.6	4.0
JC	71.8	4.5	179	63.0	37.5	19.5	12.0
JS	61.3	22.5	227	70.9	49.5	25.0	10.0
AH	72.8	18.9	314	197.0	39.0	21.0	8.7
MEAN \pm SD	74.8	13.1 \pm 3.2	213 \pm 9.4	97.7 \pm 6.5	35.5 \pm 10.6	16.7 \pm 3.5	8.6 \pm 3.9

Mean endogenous levels in $\mu\text{g. percent}$

13.1 12.1 9.6 6.0 2.8 1.5

Mean exogenous levels, corrected for endogenous decay,
in $\mu\text{g. percent}$

0 201 88.1 29.5 13.9 7.1

Table 1

Table 1 shows the results of the experiment. The data is presented in a table with 8 columns and 3 rows. The first row contains the following values: 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5. The second row contains the following values: 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5. The third row contains the following values: 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5.

1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5

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TABLE 2

PLASMA HYDROCORTISONE LEVELS DURING THE FIRST 150 MINUTES AFTER ACUTE
INTRAVENOUS INJECTIONPart I.: Uncorrected levels in μ g. percent

Subject	Time in minutes							
	15	30	45	60	80	100	120	150
JS	227	136	42.2	70.9	42.2	83.3	55.5	49.5
AH	314	219	188.0	197.0	136.8	82.1	56.0	39.0

TABLE 3

PLASMA HYDROCORTISONE LEVELS DURING AND AFTER CONSTANT INFUSION OF HYDROCORTISONE

Part II: Uncorrected levels in $\mu\text{g. percent}$

Subject	Weight	Inf. rate	Time in minutes						
			0	60	165	180	300	480	
JK	74.0 Kg.	327 $\mu\text{g./min}$	22.9	62.2	69.5	64.3	33.7	15.4	
GE	77.6	371	21.6	37.2	38.8	37.8	18.4	4.3	
RW	77.3	231	21.0	33.3	45.0	49.0	20.8	7.9	
AH	88.7	378	15.0	24.0	25.8*	25.8	20.0	4.0	
TT	95.5	227	7.2	23.6	36.2	28.8	15.2	5.5	
MEAN	SD 83.0	301	17.5	4.2	36.1	4.2	43.1	6.3	41.1
							4.5	21.6	3.8
								7.4	1.6

Mean endogenous levels in $\mu\text{g. percent}$

17.5 12.6 7.0 6.5 3.3 1.2

Mean exogenous levels, corrected for endogenous decay,
in $\mu\text{g. percent}$

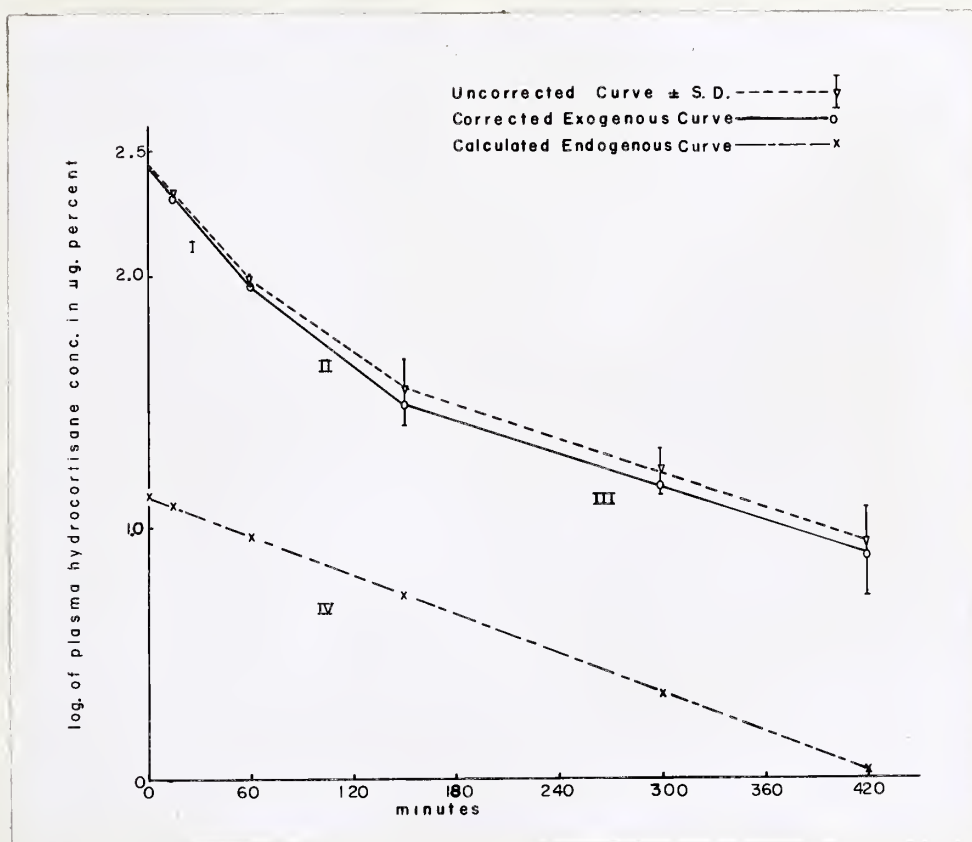
0 23.5 35.2** 18.3 6.2

* Because of error in analysis of the 165 minute sample there was no value obtained. The 180 minute value is used in order to preserve the mode of the average curve.

** The mean of the 165 and 180 minute values.

FIGURE 1.

MEAN CURVES AFTER ACUTE INTRAVENOUS INJECTION OF HYDROCORTISONE.



Equations and Half-Lives:

I. $c = 264e^{-0.0189t}$

$t_{\frac{1}{2}} = 37$ minutes

II. $c = 88.1e^{-0.0120t}$

$t_{\frac{1}{2}} = 58$ minutes

III. $c = 29.5e^{-0.00514t}$

$t_{\frac{1}{2}} = 138$ minutes

IV. $c = 13.1e^{-0.00514t}$

1. The first part of the document is a list of the names of the persons who were present at the meeting.



2. The second part of the document is a list of the names of the persons who were present at the meeting.

3. The third part of the document is a list of the names of the persons who were present at the meeting.

4. The fourth part of the document is a list of the names of the persons who were present at the meeting.

5. The fifth part of the document is a list of the names of the persons who were present at the meeting.

6. The sixth part of the document is a list of the names of the persons who were present at the meeting.

7. The seventh part of the document is a list of the names of the persons who were present at the meeting.

8. The eighth part of the document is a list of the names of the persons who were present at the meeting.

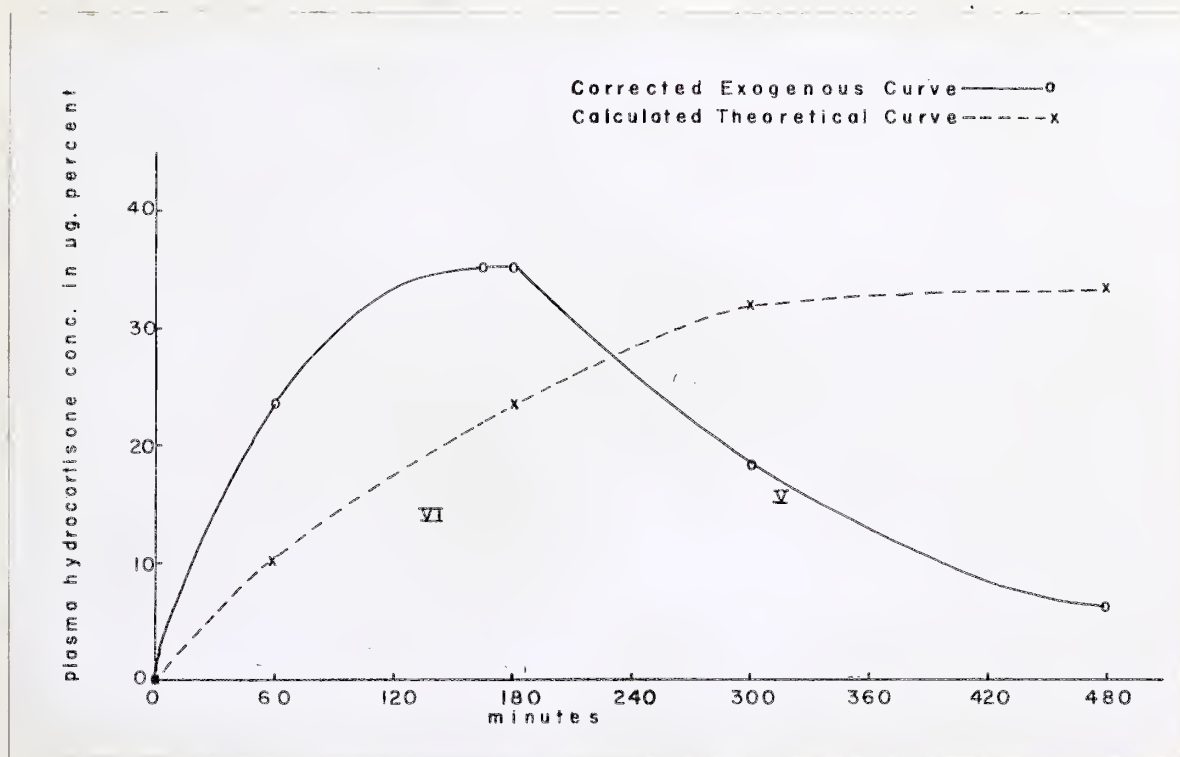
9. The ninth part of the document is a list of the names of the persons who were present at the meeting.

10. The tenth part of the document is a list of the names of the persons who were present at the meeting.

FIGURE 2

MEAN CURVES DURING AND AFTER CONSTANT INFUSION OF HYDROCORTISONE

(linear graph paper)



Equations and Half-lives:

$$V. \quad c = 35.2e^{-0.00568t}$$

$$t_{1/2} = 124 \text{ minutes}$$

$$VI. \quad c = \frac{301}{1550 (0.00568)} (1 - e^{-0.00568t})$$

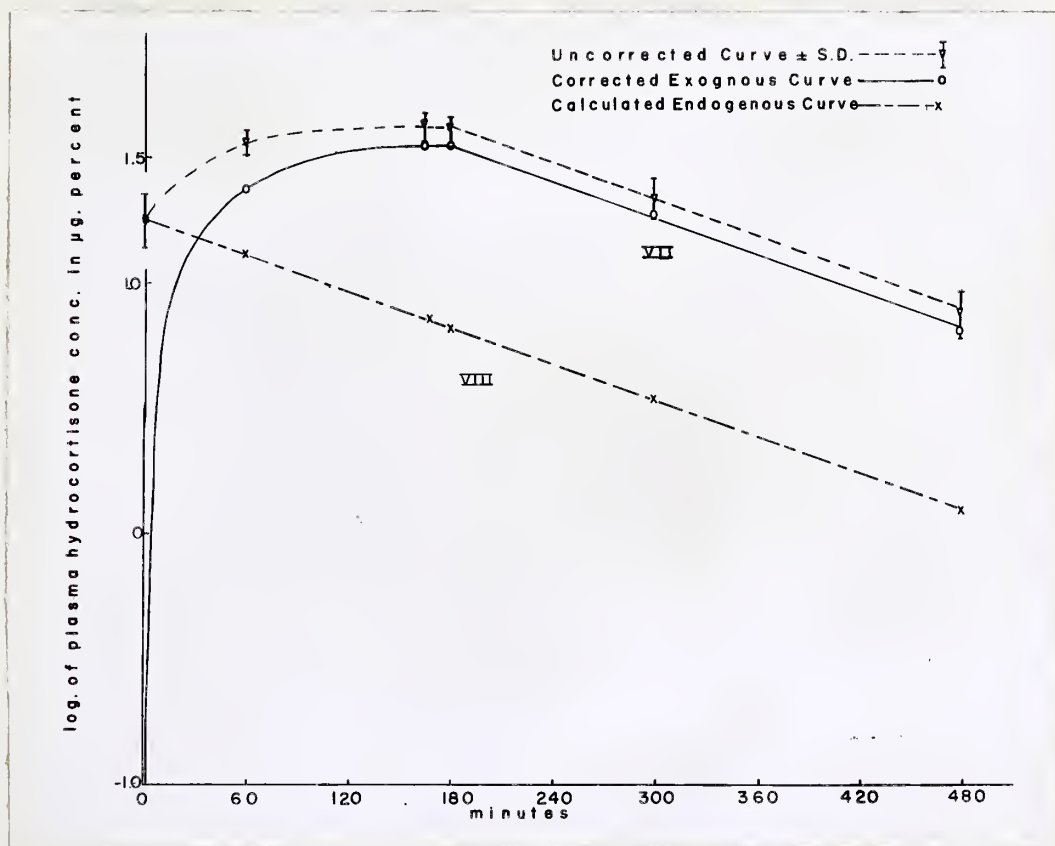
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FIGURE 3

MEAN CURVES DURING AND AFTER CONSTANT INFUSION OF HYDROCORTISONE
(semi-logarithmic graph paper)



Equations and Half-Lives:

VII. $c = 35.2e^{-0.00568t}$

$t_{1/2} = 124$ minutes

VIII. $c = 17.5e^{-0.00568t}$

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1. The first part of the paper is devoted to a general discussion of the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β .

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13. In the thirteenth part we consider the case of the existence of solutions for the system of equations (1) for arbitrary values of the parameters α and β .

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1. The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function.

2. In the second part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x$. It is shown that $f(x)$ is a linear function.

3. In the third part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^2$. It is shown that $f(x)$ is a quadratic function.

4. In the fourth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^3$. It is shown that $f(x)$ is a cubic function.

5. In the fifth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^4$. It is shown that $f(x)$ is a quartic function.

6. In the sixth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^5$. It is shown that $f(x)$ is a quintic function.

7. In the seventh part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^6$. It is shown that $f(x)$ is a sextic function.

8. In the eighth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^7$. It is shown that $f(x)$ is a septic function.

9. In the ninth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^8$. It is shown that $f(x)$ is an octic function.

10. In the tenth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^9$. It is shown that $f(x)$ is a nonic function.

11. In the eleventh part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^{10}$. It is shown that $f(x)$ is a decic function.

12. In the twelfth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^{11}$. It is shown that $f(x)$ is an undecimic function.

13. In the thirteenth part, we consider the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt + x^{12}$. It is shown that $f(x)$ is a duodecimic function.



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